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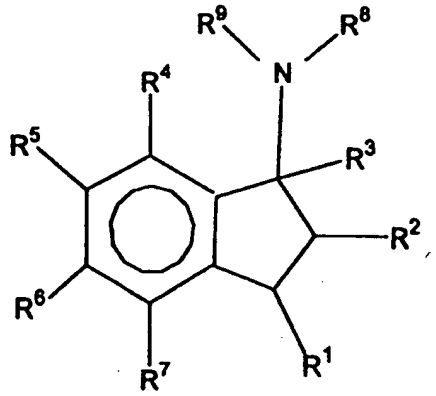

(I)

(57) Abstract

3–aminoindanones of formula (I) are described for pharmaceutical use, especially as anti–inflammatory agents and/or mast cell stabilising agents. In formula (I) R^1 to R^9 are selected from one or more of the same or different of: H, halo, hydroxy, alkoxy, aryloxy, acetoxy, carboxy, aryl, acyl, alkyl carbonyl, aryl carbonyl, hydro carbonyl, amino, amido, alkylamino, hydroxylamino, amine oxide groups, azo groups, cyano, hydrazino groups, hydrazide groups, hydrozone groups, imide groups, iminoether groups, ureyl groups, oxime, nitro, nitrate, nitrite, nitroso groups, nitrile, heterocyclic groups containing hetero atoms selected from one or more of N, O or S, aralkyl groups, mono and polybenzoid aryl groups, substituted aryl groups, thiol, thioureyl, phenylthiol groups, sulphonic acid groups, sulphoxide groups, sulphone groups, alkyl containing 1 to 10 carbon atoms, substituted alkyl, carboxylic acid containing C_1 to C_{10} which may be substituted or unsubstituted; any of: R^1 and R^2; or R^2 and R^3 together may represent a double bond; R^1 or R^2 or R^1 and R^2 together may represent oxo.

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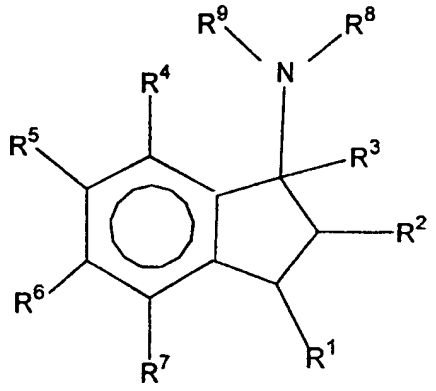
3-AMINOINDANE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

The invention relates to indane compounds, processes for their production, compositions containing them and their pharmacological use.

More particularly, the invention relates to 3-aminoindanones as anti-inflammatory agents and/or mast cell stabilising agents.

According to the invention, there is provided a compound of the formula 1



1

Wherein

R^1 to R^9

are selected from one or more of the same or different of:

H, halo, hydroxy, alkoxy, aryloxy, acetoxy, carboxy, aryl, acyl, alkyl carbonyl, hydro carbonyl, aryl carbonyl, amino, amido, alkylamino, hydroxylamino, amine oxide groups, azo groups, cyano, hydrazino groups, hydrazide groups, hydrazone groups, imide groups, iminoether groups, ureyl groups, oxime, nitro, nitrate, nitrite, nitroso groups, nitrile, heterocyclic groups containing hetero atoms selected from one or more of N, O or S, aralkyl groups, mono and polybenzoid aryl groups, substituted

aryl groups, thiol, thioureyl, phenylthiol groups, sulphonic acid groups, sulphoxide groups, sulphone groups, alkyl containing 1 to 10 carbon atoms, substituted alkyl, carboxylic acid containing C_1 to C_{10} which may be substituted or unsubstituted

any of: R^1 and R^2; or R^2 and R^3 together may represent a double bond

R^1 or R^2 or R^1 and R^2 together may represent oxo.

Preferred because of solubility, salt formation, pharmacological activity and /or ease of production are the following subsets.

In one embodiment of the invention R^1 to R^9 are selected from one or more of the same or different of:

H, hydroxy, alkoxy, aryloxy, acetoxy, alkyl carbonyl, hydrocarbonyl, amino, amido, alkylamino, hydroxylamino, amine oxide, mono and polybenzid aryl groups, substituted aryl groups, alkyl, heterocyclic groups containing hetero atoms selected from one or more of N, O.

In a preferred embodiment of the invention R^8, R^9 are one or more of the same or different of alkyl, or aryl, each of which may be substituted with one or more of the same or different of:

halo, oxo, hydroxy, alkoxy, aryloxy, acetoxy, carboxy, carbonyl, amino, amido, alkylamino, hydroxyamino, amine oxide groups, azo groups, cyano, hydrazino groups, hydrazide groups, hydrazone groups, imide groups, imino ether groups, ureyl groups, oxime, nitro, nitrate, nitrite, nitroso groups, nitrile, heterocyclic groups, aralkyl groups, mono and polybenzoid aryl groups, substituted aryl groups, thiol, thioureyl, phenyl thiol groups, sulphonic acid groups, sulphoxide groups and sulphone groups.

Preferably one or both of R^8, R^9 is alkyl of C_1 to C_{10}.

Preferably alkyl is substituted by hydroxy.

Preferably the heterocyclic groups are selected from heteroatoms containing one or more of N, O or S.

In one embodiment of the invention R^3 to R^7 are hydrogen.

Preferably R^8 is H and R^9 is COR^{10} in which R^{10} is alkyl, substituted alkyl, aryl or substituted aryl.

In a preferred arrangement R^1 represents oxo.

Alternatively R^1 represents H, OH.

Preferably R^8 and R^9 do not represent Me, PhMe, or PhEt.

In one embodiment of the invention R^8 = H and R^9 = an acetyl group. Alternatively R^8 and R^9 both represent acetyl groups.

Particularly preferred are compounds wherein R^8 represents ethyl and R^9 represents an acetyl group.

The invention especially provides the following compounds:

N-3-indan-1-onyl ethanamide (Compound I)

N-indanyl ethanamide (Compound II)

N-(tert-butyl-carbonate)-3-aminoindan-1-one (Compound IV)

N-cyclopentyl-N-3-indan-1-onyl propanmaide (Compound V)

N-cyclopentyl-N-benzoyl-3-aminoindan-1-one (Compound VI)

N-cyclopentyl-N-3-indan-1-onyl butanmaide (Compound VII)

N-cyclopentyl-N-3-indan-1-onyl heptanmaide (Compound VIII)

The invention further provides a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable carrier.

The invention also provides the use of the compounds to achieve mast cell stabilising activity and/or anti-inflammatory activity.

In addition, the invention provides a method of prophylaxis or treatment to achieve mast cell stabilising activity and/or anti-inflammatory activity by administering to a patient an effective amount of a compound of the invention.

The invention also provides processes for preparing the compounds of the invention by the process described in claims 32 to 47.

It will be appreciated that the compounds include pharmacologically acceptable salts, esters, amides, isomers and solvates thereof.

It will also be appreciated that if the compounds have one or more chircal centres they may exist as a pair of enantiomers or as a mixture of diastereomers. This may have an effect on pharmacological properties.

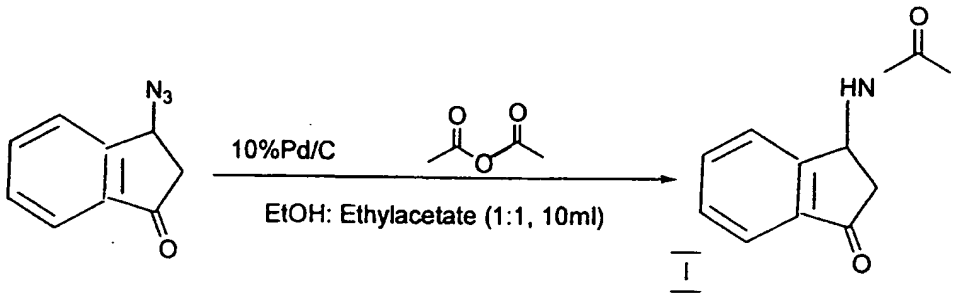
It will further be appreciated that for pharmaceutical purposes the active compounds may be formulated in any desired form using any suitable excipients and/or carriers. For example, particularly in the case for use to achieve anti-inflammatory activity the compound may be formulated in a pharmaceutical composition suitable for topical/transdermal application.

The invention will be more clearly understood from the following description thereof given by way of example only.

Detailed Description

The preparation of some of the compounds of the invention are described in detail below. Some of the starting materials used are described in our earlier applications PCT/IE96/00080, PCT/IE96/00081 and PCT/IE96/00082 the contents of which are incorporated herein for reference. Other compounds within the scope of the claims can be prepared by analogy.

Example 1 Preparation of I (Method A)



I

150 mg (8.67 mmol) of 3-Azido-indan-1-one was dissolved in 10 ml of an ethanol/ethyl acetate mixture (1:1) and stirred at room temperature. 150 mg of 10% palladium on charcoal was added to the mixture followed by 176.5 mg (17.34 mmol) of acetic acid. The reaction mixture was then put under a hydrogen atmosphere using a Kips apparatus (40% Hydrochloric acid dropped onto Zinc granules) and monitered by TLC to completion (3 hours). The reaction mixture was filtered and evaporated to dryness to give a yellow oil. This oil was purified by eluting on a column of flash silica to give a yellow solid (9/1: petroleum spirit/ethyl acetate grading to 1/4: petroleum spirit/ethyl acetate) and subsequent recrystallisation from ethyl acetate yielding compound I as white needles, (80 mg, 61%) mp 152.1-152.8°C.

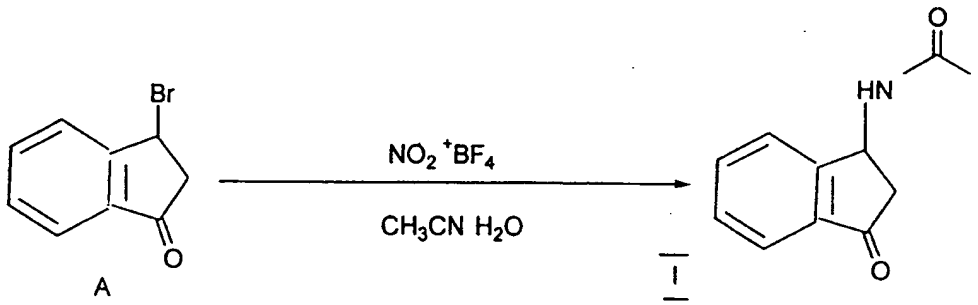
^{1}H nmr ($CDCl_3$, 400 MHz)

δ_H 2.02 (3H, s, $C\underline{H}_3$), 2.45 (1H, dd, J=3.4 & 19 Hz, C$\underline{H}$ of CH_2), 3.14 (dd, J=7.6 and 19 Hz, C$\underline{H}$ of CH_2), 5.61 (1H, m, NHC$\underline{H}$CH_2), 6.4 (1H, broad, N$\underline{H}$), 7.41-7.68 (4H, m, aromatics).

^{13}C nmr ($CDCl_3$, 75.47 MHz)

δ_C 22.7 (CH_3), 44.3 (CH_2), 46.9 (CH), 122.8, 125.6, 128.8, 135.0 (4 x Ar-CH), 136.2, 153.5, (2 x Ar-C), 202.9, (C=O).

Example 2 Preparation of I (Method B)



Nitronium tetrafluoroborate (250 mg, 1.88 mmol) was dispersed in a clean dry necked round bottomed flask at 0°C under nitrogen. To this was added 3-bromoindanone (200 mg, 0.95 mmol) in clean dry acetonitrile (20 ml). The reaction was stirred at 0°C for 6 hours and quenched by the addition of water (20 ml). The product was isolated by column chromatography over silica gel and petroleum spirit : ethyl acetate (1:4) and recrystallised from ethyl acetate to give compound I as white needles (90 mg, 50.2%).

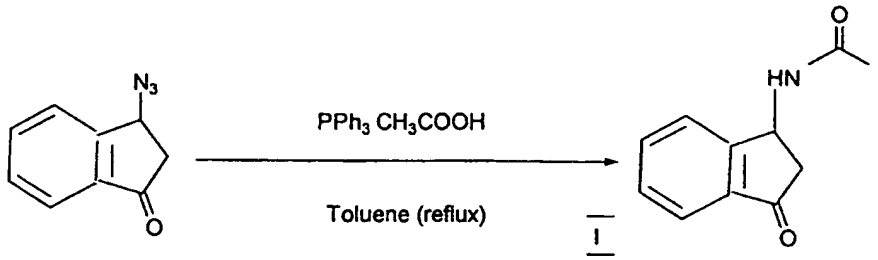
^1H nmr ($CDCl_3$, 400 MHz)

δ_H 2.02 (3H, s, $C\underline{H}_3$), 2.45 (1H, dd, J=3.4 & 19 Hz, $C\underline{H}$ of CH_2), 3.14 (dd, J=7.6 and 19 Hz, $C\underline{H}$ of CH_2), 5.61 (1H, m, $NHC\underline{H}CH_2$), 6.4 (1H, broad, $N\underline{H}$), 7.41-7.68 (4H, m, aromatics).

^{13}C nmr ($CDCl_3$, 75.47 MHz)

δ_C 22.7 (CH_3), 44.3 (CH_2), 46.9 (CH), 122.8, 125.6, 128.8, 135.0 (4 x Ar-CH), 136.2, 153.5, (2 x Ar-C), 202.9, (C=O).

Example 3 Preparation of I (Method C)



I

346 mg (2 mmol) of the 3-Azido-indan-1-one was dissolved in 10 ml of anhydrous toluene. To this stirring solution was added 262 mg (2 mmol) of triphenylphosphine and 57.6 mg (2.4 mmol) of acetic acid. The mixture was refluxed for 12 hours and then cooled to room temperature and washed with 10 ml of 5% $NaHCO_3$ solution. The organic layer was separated and put on a column of flash silica and eluted with pet spirit : ethyl acetate (1:4) to give a yellow oil which was recrystallised from ethyl acetate to give compound I as white needles, 50 mg (15.3%).

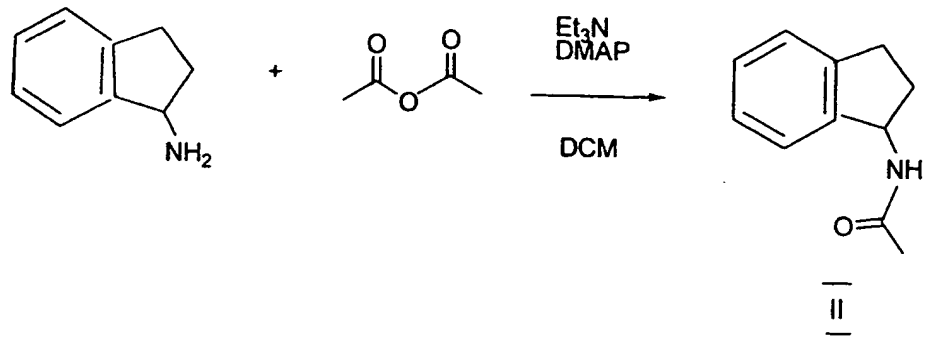
^1H nmr ($CDCl_3$, 400 MHz)

δ_H 2.02 (3H, s, $C\underline{H}_3$), 2.45 (1H, dd, J=3.4 & 19 Hz, C$\underline{H}$ of CH_2), 3.14 (dd, J=7.6 and 19 Hz, C$\underline{H}$ of CH_2), 5.61 (1H, m, NHC$\underline{H}CH_2$), 6.4 (1H, broad, N$\underline{H}$), 7.41-7.68 (4H, m, aromatics).

^{13}C nmr ($CDCl_3$, 75.47 MHz)

δ_C 22.7 (CH_3), 44.3 (CH_2), 46.9 (CH), 122.8, 125.6, 128.8, 135.0 (4 x Ar-CH), 136.2, 153.5 (2 x Ar-C), 202.9, (C=O).

Example 4 Preparation of II



II

1-Aminoindan (1g, 7.5 mmol) was dispersed in clean dry DCM (15 ml) and triethylamine (2.1 ml, 1.53 g, 15.1 mmol). To this solution was added acetic anhydride (1.5 ml, 1.6 g, 16 mmol) and DMAP (0.92 g, 7.5 mmol). The mixture was allowed to stir at room temperature for 1 hour and passed through a plug of silica eluting with petroleum ether: ethyl acetate (1.4) (0.97 g, 74%). Compound II was formed.

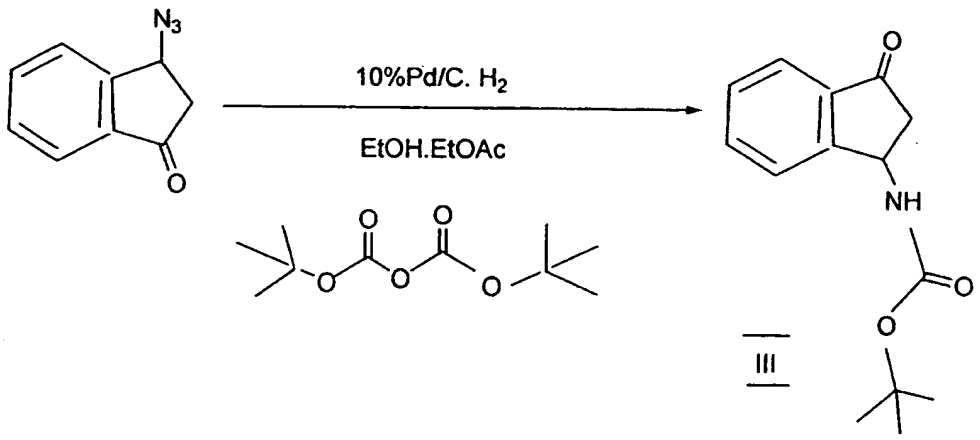
^{1}H nmr ($\delta CDCl_3$, 400 MHz)

1.77–1.89 (1H, m, C<u>H</u> of CH_2), 2.03 (3H, s, CH_3), 2.55-2.64 (1H, m, C<u>H</u> of CH_2), 2.83-2.91 (1H, m, C<u>H</u> of CH_2), 2.95-3.03 (1H, m, C<u>H</u> of CH_2), 5.47 (1H, qm, J=7.7Hz, C<u>H</u>NH), 5.85 (1H, bs, N<u>H</u>), 7.23-7.31 (4H, m, Ar-C<u>H</u>).

^{13}C nmr ($CDCl_3$, 75.47 MHz)

22.9 (CO<u>C</u>H_3), 29.8, 33.6 (2 x <u>C</u>H_2), 54.3 (<u>C</u>H), 123.6, 124.4, 126.3, 127.5 (4 x Ar-<u>C</u>H), 142.7, 143.0 (2 x Ar-<u>C</u>), 169.4 (<u>C</u>OCH_3).

Example 5 Preparation of III



3-Azido-indan-1-one (100mg, 0.578 mmol) was dispersed in EtOH:EtOAc (1:1, 3ml) and triethylamine (2.1 ml, 1.53 g, 15.1 mmol). To this solution was added 10% palladium over charcoal (100 mg), di-tert-butyl-dicarbonate (0.25 g, 1.16 mmol) and the mixture was stirred under hydrogen for two hours. The crude mixture was passed through a plug of silica eluting with petroleum ether: ether acetate (1:4) (0.12 g, 86%). Compound III was formed.

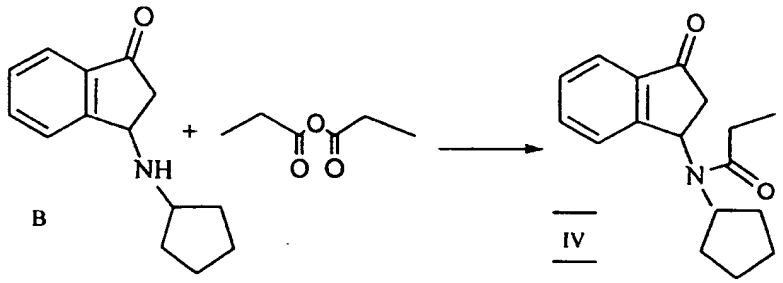
^{1}H nmr (δCDC1$_3$, 400 MHz)

1.42 (9H, s, 3 x CH_3), 2.45 (1H, d, J = 19.1 Hz, C<u>H</u> of CH_2), 3.12 (1H, q, J = 6.8Hz, 12.3 Hz, C<u>H</u> of CH_2), 5.04-5.32 (2H, m, C<u>H</u>NH & N<u>H</u>), 7.26 – 7.67 (4H, m, Ar-C<u>H</u>).

^{13}C nmr ($CDC1_3$, 75.47 MHz)

28.2 (3 x <u>C</u>H$_3$), 44.9 (<u>C</u>H$_2$), 48.6 (<u>C</u>H), 79.9 (q<u>C</u>), 123.1, 125.8, 128.9, 135.1 (4 x Ar-<u>C</u>H), 136.4, 154.1 (2 x Ar-<u>C</u>), 155.6, 203.3 (2 x <u>C</u>O).

Example 6 Synthesis of IV



Compound B (500mg, 0.232 mmol) was dissolved in DCM (10ml) and to this was added triethylamine (0.47g, 0.65ml, 4.65mmol) and propionic anhydride (0.61ml, 4.65mmol). Then to this stirring solution DMAP (catalytic quantities) was added. The reaction mixture was allowed to stir at room temperature for 3 hours. To the reaction solution was added 2M aqueous HCl (5ml) and 10ml DCM. The organic layer was obtained and washed with water. To the organic was added to a 10% solution of $NaHCO_3$ (30ml). The organic phase was collected and the aqueous layer was washed with DCM. All the organic layers were combined and dried over Na_2SO_4. The crude reaction was then passed through a plug of flash silica, eluting with petroleum ether 100% and grading to petroleum ether : ethyl acetate 1:4. The product Compound IV was obtained as a white solid (217mg, 34.8%).

^1H nmr ($\delta CDCl_3$, 400 MHz)

0.93 (3H, bs, C<u>H</u>$_3$), 1.6 – 2.96 (12H, m, 6x C<u>H</u>$_2$), 4.49 (1H, s, C<u>H</u>), 4.88(1H,s, C<u>H</u>),7.38 – 7.61 (4H, m, Ar – C<u>H</u>)

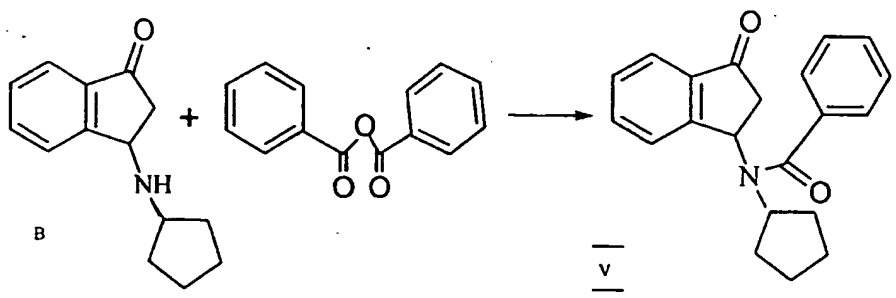
Low resolution mass Spectrum

$C_{17}H_{21}NO_2$ requires M^+271, found M^+ 271

^{13}C nmr ($CDCl_3$, 75.47 MHz)

9.3 (<u>C</u>H$_3$), 24.2, 24.2, 27.6, 30.6, 31.1, 43.1 (6 x <u>C</u>H$_2$), 56.4, 57.2 (2 x <u>C</u>H), 122.8, 124.2, 129.5, 134.6 (4 x Ar – <u>C</u>H), 137.5, 156.6 (2 x Ar – <u>C</u>), 172.6, 203.1 (2 x <u>C</u>=O)

Example 7 Synthesis of V



Compound B (500mg, 0.232 mmol) was dissolved in DCM (10ml) and to this was added triethylamine (0.47g, 0.65ml, 4.65 mmol) and benzoic anhydride (1.05g, 4.65mmol). Then to this stirring solution DMAP (catalytic quantities) was added. The reaction mixture was allowed to stir at room temperature for 3 hours. To the reaction solution was added 2M aqueous HCl (5ml) and 10ml DCM. The organic layer was obtained and washed with water. To the organic layer was added a 10% solution of $NaCHO_3$ (30ml). The organic phase was collected and the aqueous layer was washed with DCM. All the organic layers were combined and dried over Na_2SO_4. The crude reaction was then passed through a plug of flash silica, eluting with petroleum ether 100% and grading to petroleum ether : ethyl acetate 1:4. The product Compound V was obtained as a white solid (339mg, 45.8%).

^1H nmr ($\delta CDCl_3$, 400MHz)

0.88 – 1.99 (8H, m, 4 x $C\underline{H}_2$), 2.87 – 3.06 (2H, m, $C\underline{H}_2$), 3.38 (1H, s, C<u>H</u>), 4.77 (1H, s, C<u>H</u>), 7.41 – 8.00 (9H, m, Ar – C<u>H</u>)

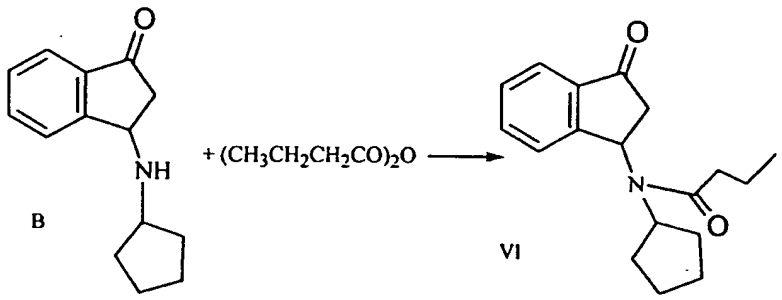
Lower resolution mass Spectrum

$C_{21}H_{21}NO_2$ requires M^+319, Found M^+319

^{13}C nmr ($CDCl_3$, 75.47 MHz)

23.4, 23.5, 31.0, 31.7, 42.3 (5 x $\underline{C}H_2$), 53.8, 57.3 (2 x $\underline{C}H$), 123.5, 126.8, 127.9, 127.9 129.3, 129.6, 129.6, 131.7, 134.9 (9 x Ar – $\underline{C}H$), 133.2, 136.7, 151.8 (3 x Ar –C), 171.3, 202.3 (2 x $\underline{C}$=O)

Example 8 Synthesis of VI



Compound B (1.5g, 0.696 mmol) was dissolved in DCM (10ml) and to this was added triethylamine (0.19g, 0.14ml, 1.39 mmol) and butyric anydride (0.23ml, 1.39 mmol). Then to this stirring solution DMAP (catalytic quantities) was added. The reaction mixture was allowed to stir at room temperature for 3 hours. To the reaction solution was added 2M aqueous HCl (5ml) and 10ml DCM. The organic layer was obtained and washed with water. To the organic was added to a 10% solution of $NaHCO_3$ (30ml). The organic phase was collected and the aqueous layer was washed with DCM. All the organic layers were combined and dried over Na_2SO_4. The crude reaction was then passed through a plug of flash silica, eluting with petroleum ether 100% and grading to petroleum ether : ethyl acetate 1:4. Compound VI was formed.

^1H nmr ($\delta CDCl_3$, 400 MHz)

0.96 (3H, t, J=7.52Hz, $C\underline{H}_3$), 0.89 – 2.16 (10H, m, 5 x $C\underline{H}_2$), 2.30 (2H, t, J=7.04Hz, $COC\underline{H}_2CH_2$), 2.88 (1H, bs, 1 each $CHCO\underline{H}_2$), 3.08 (1H, bs, 1 each $CHCOC\underline{H}_2$), 4.35 (1H, bs, C<u>H</u>), 4.66 (1H, bs, C<u>H</u>), 7.28 – 7.76 (4H, m, Ar – C<u>H</u>)

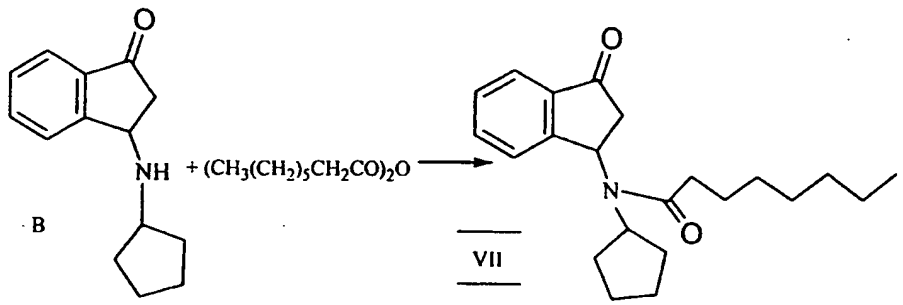
Low resolution mass Spectrum

$C_{18}H_{23}NO_2$ requires M^+ 291, Found M^+ 291

^{13}C nmr ($CDCl_3$, 75.47 MHz)

13.3 ($\underline{C}H_3$), 18.5, 23.6, 25.1, 25.5, 29.1, 29.6, 30.3, 30.5, 35.4, 36.0, 36.6, 36.8, 41.9, 42.4 (7 x $\underline{C}H_2$), 51.7, 55.7, 56.7, 58.6, (2 x N$\underline{C}$H), 122.6, 123.0, 123.3, 125.1, 127.4, 128.9, 134.0, 134.9 (4 x Ar – $\underline{C}$H), 136.1, 154.7 (2 x Ar – $\underline{C}$), 178.2, 202.8, (2 x $\underline{C}$=O)

Example 9 Synthesis of VII



Compound B (1.5g, 0.696 mmol) was dissolved in DCM (10ml) and to this was added triethylamine (0.19g, 0.14ml, 1.39mmol) and heptanoic anhydride (0.36ml, 1.39mmol). Then to this stirring solution DMAP (catalytic quantities) was added. The reaction mixture was allowed to stir at room temperature for 3 hours. To the reaction solution was added 2M aqueous HCl (5ml) and 10ml DCM. The organic layer was obtained and washed with water. To the organic was added to a 10% solution of $NaHCO_3$ (30ml). The organic phase was collected and the aqueous layer was washed with DCM. All the organic layers were combined and dried over Na_2SO_4. The crude reaction was then passed through a plug of flash silica, eluting with petroleum ether 100% grading to petroleum ether : ethyl acetate 1:4. The product Compound VII was obtained as a white solid.

^1H nmr ($\delta CDCl_3$, 400 MHz)

0.86 (3H, t, J=3Hz, $C\underline{H}_3$), 1.18 – 2.29 (16H, m, 8 x $C\underline{H}_2$), 2.33 (2H, bs, $COCH_2C\underline{H}_2$), 2.86 (1H, bs, 1 each $CHCOCH_2$), 3.06 (1H, bs, 1 each $CHCOC\underline{H}_2$), 4.29 (1H, bs, C<u>H</u>), 4.64 (1H, bs, C<u>H</u>), 7.38 – 7.61 (4H, m, Ar – C<u>H</u>)

Low resolution mass Spectrum

$C_{22}H_{31}NO_2$ requires M^+ 341, Found M^+ 341

^{13}C nmr ($CDCl_3$, 75.47 MHz)

13.3 ($\underline{C}H_3$), 24.3, 24.7, 25.1, 25.5, 28.3, 28.5, 28.6, 28.7, 29.1, 29.6, 30.3, 30.5, 30.9, 31.1, 31.2, 33.5, 34.1, 34.9, 41.9, 42.4, (10 x $\underline{C}H_2$), 55.6, 56.6, 58.5, 59.9, (2 x N$\underline{C}$H), 122.9, 123.2, 123.2, 125.1, 127.3, 128.9, 134.0, 134.8 (4 x Ar – $\underline{C}$H), 154.7, 171.8 (2 x Ar – C), 176.3, 202.7 (2 x $\underline{C}$=O)

PHARMACOLOGY

Introduction

The indane compounds according to the invention have mast cell stabilising activity, smooth muscle relaxing activity, and anti-inflammatory activity. The compounds are, therefore, potential anti-asthmatic agents with bronchodilator activity. The mast cell stabilising activity of the compounds suggests their potential use in the treatment of allergic rhinitis, allergic conjunctivitis and other anaphylactic or allergic conditions. The anti-flammatory activity may have applications in gout, rheumatic diseases, ankylosing spondylitis, polymyalgia rheumatica, temporal arteritis, polyarteritis nodosa, polymyositis and systemic lupus arteriosis and other inflammatory conditions. Topical applications may includes: atopic excema, weeping excemas, psoriasis, chronic discoid lupus erythematosus, lichen simplex chronicus, hypertrophic lichen planus, palmar plantar pustulosis. They may also have potential in the treatment of some malignant diseases and as immunosuppressants.

The smooth muscle relaxing activity of the compounds may have potential in the treatment of hypertension and peripheral vascular disease, such as intermittent claudication and Reynaud's syndrome, as well as other cardiovascular disorders, such as congestive heart failure, angina pectoris, cerebral vascular disease and pulmonary hypertension. Such compounds are also indicated for potential use in the treatment of certain disorders of the gastro-intestinal tract, such as diverticular disease and irritable bowel syndrome. Similarly, these compounds may have potential as agents for the treatment of disorders of the genito-urinary tract, such as premature labour, incontinence, renal colic and disorders associated with the passage of kidney stones. Members of this group of compounds may also have potential as diuretics analgesics, antipyretics, local anaesthetics, central nervous system depressants and hypoglycaemic agents.

Mouse Ear Oedema Model

The mouse ear oedema model was performed using Laca mice (25-35g), of either sex. The animals were sedated with fentanyl/fluanisone (Hypnorm, Janssen). One ear was treated by the topical application of one of a range of test compounds or dexamethasone (all at 300 μg per ear in acetone). After 30 minutes, oedema was induced by the topical application of arachidonic acid (10 μl at 0.4g/ml in acetone). The width of each ear was measured, both before and 60 minutes after the induction of oedema, using a micrometer screw gauge. Ear oedema was calculated by comparing the ear width before and after induction of oedema and expressed as percentage normal.

Values are expressed as the percentage increase in ear thickness 1 hour after administration of arachidonic acid and solvent controls (n=6 except Compound II, n=4).

Compound I

	Control (-ve)	Dexamethasone	I
δ%	75.0	43.2	25.0
δ%	67.6	25.0	28.6
δ%	80.0	51.4	27.8
δ%	58.8	32.4	30.6
δ%	85.3	62.5	31.4
δ%	47.1	35.1	35.1
Mean	69.0	41.6	29.7
SEM	5.8	5.6	1.4

Compound II

	Control (-ve)	Dexamethasone	II
δ%	75.0	43.2	25.0
δ%	67.6	25.0	27.9
δ%	80.0	51.4	32.4
δ%	58.8	32.4	36.8
δ%	85.3	62.5	
δ%	47.1	35.1	
Mean	69.0	41.6	30.5
SEM	5.8	5.6	2.6

Modified Protocol of Mouse Ear Oedema.

Arachidonic Acid-induced Mouse Ear Oedema

Methods

Male Laca mice (23 – 35g) were sedated with sagatal. The right ears of groups of mice were treated by the topical application of indomethacin, IV or V (300μg) in acetone. One group of mice received acetone alone (negative control) on their right ears. Compounds/acetone were applied in a volume of 10μl (20μl total) each to the inner and outer aspects of the ear. One hour later, arachidonic acid (0.5mg) was applied to the right ears of the mice, in a volume of 10μl (20 μl total) each to the inner and outer aspects of the ear. One hour later, the mice were killed by cervical dislocation and 5mm biopsy punches were taken from both the right and left ears. Oedema was expressed as a percentage change in weight of arachidonic acid-treated ears versus untreated ears.

Results

Compound	Mean %	SEM	n (number)
Indomethacin	14.1	3.9	10
IV	47.1	14.3	5
V	18.6	2.2	4
Solvent Control	101	15.9	9

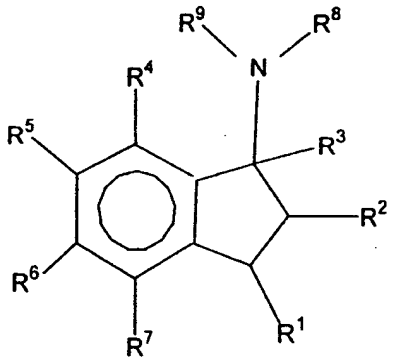
Mast Cell: (Protocol as original)

Compound	% Inhibition of Histamine Release	N (number)
IV	92.5 ± 9.6	3
V	18.7 ± 6.7	3

The invention is not limited to the embodiments hereinbefore described which may be varied in detail.

CLAIMS

1. A pharmaceutical compound of formula 1



1

wherein

R^1 to R^9

are selected from one or more of the same or different of:

H, halo, hydroxy, alkoxy, aryloxy, acetoxy, carboxy, aryl, acyl, alkyl carbonyl, aryl carbonyl, hydro carbonyl, amino, amido, alkylamino, hydroxylamino, amine oxide groups, azo groups, cyano, hydrazino groups, hydrazide groups, hydrozone groups, imide groups, iminoether groups, ureyl groups, oxime, nitro, nitrate, nitrite, nitroso groups, nitrile, heterocyclic groups containing hetero atoms selected from one or more of N, O or S, aralkyl groups, mono and polybenzoid aryl groups, substituted aryl groups, thiol, thioureyl, phenylthiol groups, sulphonic acid groups, sulphoxide groups, sulphone groups, alkyl containing 1 to 10 carbon atoms, substituted alkyl, carboxylic acid containing C_1 to C_{10} which may be substituted or unsubstituted.

any of: R^1 and R^2; or R^2 and R^3 together may represent a double bond

R^1 or R^2 or R^1 and R^2 together may represent oxo.

2. A compound as claimed in claim 1 wherein R^1 to R^9 are selected from one or more of the same or different of:

H, hydroxy, alkoxy, aryloxy, acetoxy, alkyl carbonyl, hydrocarbonyl, amino, amido, alkylamino, hydroxylamino, amine oxide, mono and polybenzid aryl groups, substituted aryl groups, alkyl, heterocyclic groups containing hetero atoms selected from one or more of N, O.

3. A compound as claimed in claim 1 or 2 wherein R^8, R^9 are one or more of the same or different of alkyl, or aryl, each of which may be substituted with one or more of the same or different of halo, oxo, hydroxy, alkoxy, aryloxy, acetoxy, carboxy, carbonyl, amino, amido, alkylamino, hydroxyamino, amine oxide groups, azo groups, cyano, hydrazino groups, hydrazide groups, hydrazone groups, imide groups, imino ether groups, ureyl groups, oxime, nitro, nitrate, nitrite, nitroso groups, nitrile, heterocyclic groups, aralkyl groups, mono and polybenzoid aryl groups, substituted aryl groups, thiol, thioureyl, phenyl thiol groups, sulphonic acid groups, sulphoxide groups and sulphone groups.

4. A compound as claimed in claim 3 wherein one or both of R^8, R^9 is alkyl of C_1 to C_{10}.

5. A compound as claimed in claim 4 wherein alkyl is substituted by hydroxy.

6. A compound as claimed in claim 3 wherein the heterocyclic groups are selected from heteroatoms containing one or more of N, O or S.

7. A compound as claimed in any of claims 1 to 6 wherein R^3 to R^7 are hydrogen.

8. A compound as claimed in any of claims 1 to 7, wherein R^8 is H and R^9 is COR^{10} in which R^{10} is alkyl, substituted alkyl, aryl or substituted aryl.

9. A compound as claimed in any of claims 1 to 8, wherein R^1 represents oxo.

10. A compound as claimed in any of claims 1 to 8 wherein R^1 represents H, OH.

11. A compound as claimed in any of claims 1 to 8 wherein R^1 represents H.

12. A compound as claimed in any preceding claim wherein R^8 and R^9 do not represent Me, PhMe, or PhEt.

13. A compound as claimed in any preceding claim wherein R^8 = H and R^9 = an acetyl group.

14. A compound as claimed in any of claims 1 to 12, wherein R^8 and R^9 both represent acetyl groups.

15. A compound as claimed in any of claims 1 to 12, wherein R^8 represents ethyl and R^9 represents an acetyl group.

16. N-3-indan-1-onyl ethanamide

17. N-indanyl ethanamide

18. N-(tert-butyl-carbonate)-3-aminoindan-1-one

19. N-cyclopentyl-N-3-indan-1-onyl propanmaide

20. N-cyclopentyl-N-benzoyl-3-aminoindan-1-one

21. N-cyclopentyl-N-3-indan-1-onyl butanmaide

22. N-cyclopentyl-N-3-indan-1-onyl heptanmaide

23. A compound of formula 1 substantially as hereinbefore described with reference to the examples.

24. A pharmaceutical composition comprising a compound of any of claims 1 to 23 and a pharmaceutically acceptable carrier.

25. A pharmaceutical composition substantially as hereinbefore described with reference to the examples.

26. Use of a compound as claimed in any of claims 1 to 23 to achieve mast cell stabilising activity and/or anti-inflammatory activity.

27. Use of a compound as claimed in any of claims 1 to 23 to achieve mast cell stabilising activity.

28. Use of a compound as claimed in any of claims 1 to 23 to achieve anti-inflammatory activity.

29. Use substantially as hereinbefore described with reference to the Examples.

30. A compound of formula 1 as claimed in any of claims 1 to 23 to achieve mast cell stabilising activity and/or anti-inflammatory activity.

31. A method of prophylaxis or treatment to achieve mast cell stabilising activity and/or anti-inflammatory activity by administering to a patient an effective amount of a compound of formula 1 as defined in any of claims 1 to 23.

32. A process for preparing a compound as claimed in any of claims 1 to 23 by reacting 3-bromo indanone with sodium azide and reacting the isolate 3-azido-indan-1-one with 10% Pd/C under hydrogen in the presence of acetic anhydride.

33. A process as claimed in claim 32 using alkyl or aryl anhydrides.

34. A process for preparing a compound of any of claims 1 to 23 by reacting 3-bromoindanone with nitronium tetrafluoroborate in acetonitrile followed by quenching with H_2O.

35. A process as claimed in claim 34 wherein 3-bromoindanone is reacted with nitronium tetrafluoroborate in the presence of alkyl or aryl nitriles.

36. A process for preparing a compound of any of claims 1 to 23 by reacting 3-azido indan-1-one with triphenylphosphine and acetic acid.

37. A process as claimed in claim 36 wherein 3-azido indan-1-one is reacted with triphenylphosphine and alkyl or aryl carboxylic acids.

38. A process for preparing compounds of any of claims 1 to 23 in which 3 bromoindanone is reacted with alkylamines (C 1-10) in the presence of triethylamine.

39. A process as claimed in claim 38 wherein the reaction is carried out with alkyl or aryl anhydrides in the presence of DMAP.

40. A process as claimed in claim 38 wherein the reaction is carried out with alkylhalides in the presence of strong base.

41. A process for preparing a compound of any of claims 1 to 23 by reduction of a double bond and/or ketone functional groups, particularly using a catalyst, especially Palladium over activated charcoal which may also include a concentrated aqueous acid such as HCl.

42. A process as claimed in claim 41 wherein the reduction of ketone functional groups is achieved by using sodium borohydride.

43. A process as claimed in claim 41 wherein the reduction of ketone functional groups is achieved by using hydrazine hydrate.

44. A process as claimed in claim 41 wherein the reduction of ketone functional groups is achieved by using sodium cyanoborohydride.

45. A process as claimed in claim 41 wherein the reduction of ketone functional groups is achieved with lithium tritertbutoxyaluminohydride or by using lithium aluminium hydride as reducing agent.

46. A process as claimed in any of claims 41 to 45 including the step of N-alkylation or N-acylation of the coupled products.

47. A process substantially as hereinbefore described with reference to the examples.

48. A compound of formula 1 whenever prepared by any of the process of any of claims 32 to 47.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/IE 98/00040

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C233/06 C07C233/32 C07C271/24 A61K31/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	S. RAULT ET AL : "Une synthèse simple des premières amino-3 indanones-1" BULLETIN DE LA SOCIETE CHIMIQUE DE FRANCE., no. 6, 1987, pages 1079-1083, XP002078691 PARIS FR see page 1080; examples 8-10 ---	1,8,9,13
X	S. RAULT ET AL: "Indano(1,2-b)aziridine : I-Etude des conditions de synthèse" BULLETIN DE LA SOCIETE CHIMIQUE DE FRANCE., vol. 127, no. 2, 1990, pages 316-323, XP002078692 PARIS FR see page 317 - page 318 ---	1,8,9,13
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 September 1998	07/10/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Voyiazoglou, D

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interr. ...al Application No
PCT/IE 98/00040

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	H. E. SMITH ET AL : "Optically active amines-X. " TETRAHEDRON LETTERS, vol. 26, 1970, pages 107-118, XP002078693 OXFORD GB see page 110; example 9A	1
X	WO 96 21640 A (TEVA) 18 July 1996 see page 50 - page 51; claim 1; examples 17-19	1,17
X	DE 28 12 578 A (ELI LILLY) 5 October 1978 see claim 1	1
X	FR 2 042 360 A (DEUTSCHE GOLD UND SILBER) 12 February 1971 see page 16, last paragraph; claims 1,7	1,6,26, 30
X	I. ZELENSKY ET AL : "Study of mechanism of cathodic reduction of some indane keto-isonitroso derivatives" COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS., vol. 35, 1970, pages 644-650, XP002078699 PRAGUE CS see page 650, last paragraph	1

3

INTERNATIONAL SEARCH REPORT

Int. ational application No.
PCT/IE 98/00040

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 31
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 31 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/IE 98/00040

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